

Correlations Among Time and Frequency Domain Measures of Heart Period Variability Two Weeks After Acute Myocardial Infarction

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Several hundred fifteen participants from a multicenter natural history study of acute myocardial infarction were studied (1) to determine the correlations among time and frequency domain measures of heart period variability, (2) to determine the correlations between the measures of heart period variability and previously established postinfarction risk predictors, and (3) to determine the predictive value of time domain measures of heart period variability for death during follow-up after acute myocardial infarction. Twenty-four hour electrocardiographic recordings obtained 11 ± 3 days after acute myocardial infarction were analyzed and 11 measures of heart period variability were computed. Each of 4 bands in the heart period power spectrum had 1 or 2 corresponding variables in the time domain that correlated with it so strongly ($r \geq 0.90$) that the variables were essentially equivalent: ultra low frequency power with SDNN* and SDANN index,* very low frequency power and low-frequency power with SDNN index,* and high-frequency power with r-MSSD* and pNN50.* As expected from theoretical considerations, SDNN and the square root of total power were almost perfectly correlated. Correlations between the time and frequency domain measures of heart period variability and previously identified postinfarction risk predictors, e.g., left ventricular ejection fraction and ventricular arrhythmias, are remarkably weak. Time domain measures of heart period variability, especially those that measure ultra low or low-frequency power, are strongly and independently associated with death during follow-up.

* Defined in Table II.

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In 1987, we showed that the standard deviation of normal RR intervals over 24 hours (SDNN) predicts all-cause mortality after myocardial infarction independently of the major risk factors identified by the Multicenter Post Infarction Program (MPIP), i.e., New York Heart Association functional class, pulmonary rates in the coronary care unit phase of the infarction, radionuclide left ventricular ejection fraction, and the frequency of ventricular arrhythmias.¹ However, SDNN measures all sources of heart period variability and thus provides little insight into the physiologic mechanisms causing risk. Power spectral analysis of heart period variability has been used to evaluate the autonomic nervous system in normal human subjects^{2,3} and in patients after myocardial infarction.⁴ In 1992, we reported that several frequency domain (power spectral) measures of heart period variability are also significantly associated with death during follow-up after myocardial infarction.⁵ Other time domain measures of heart period variability have been suggested as predictors of mortality, but have not been evaluated in a large patient group.⁶ The purposes of this study were (1) to determine the correlations among time and frequency domain measures of heart period variability, (2) to determine the correlations between the measures of heart period variability and previously established postinfarction risk predictors, and (3) to determine the predictive value of time domain measures of heart period variability for death during follow-up after myocardial infarction.

METHODS

Study design: To measure heart period variability after myocardial infarction, we reanalyzed the 24-hour continuous electrocardiographic recordings from the MPIP, a longitudinal study that enrolled 867 patients from diverse geographies and categories of hospitals.⁷ Left ventricular function, arrhythmia and myocardial ischemia were assessed 2 weeks after myocardial infarction and related to mortality during 2 to 4 years of follow-up. These features make the results of MPIP widely generalizable to the general population of patients with recent myocardial infarction in the United States. The details of enrollment, measurement of baseline variables, quality control procedures, and follow-up for MPIP have been described previously.^{7,8}

Processing of 24-hour Holter tapes: The 24-hour electrocardiographic recordings were reprocessed for heart period variability using recently described methods.⁹⁻¹¹ Briefly, 24-hour recordings were A/D converted on a Marquette 8000 scanner at 128 samples per sec-

TABLE I Reasons Tapes Were Excluded from the Study

Tape not recorded	47
Tape deteriorated in storage	36
Insufficient data*	48
Atrial fibrillation	7
Other rhythm disturbance	14

*To qualify, a tape was required to have 12 hours or more of analyzable data with ≥ 2.5 hours of analyzable data during the nighttime period (50%) and ≥ 7.0 hours of analyzable data during the daytime period (50%). At least half the data had to be sinus rhythm during the nighttime period, during the daytime period, and overall.

ond. Initial QRS labeling and editing were done with the standard Marquette algorithms (version 5.7 software). Then, the data files were transferred via high speed link from the Marquette scanner to a Sun workstation where, using algorithms developed at Columbia University, a second stage of editing was done to find and correct errors that could adversely affect measurement of heart period variability.¹² For a tape to be eligible for this study we required that it have ≥ 12 hours of analyzable data and have at least half of the nighttime and half of the daytime periods analyzable. Also, at least half of the daytime, half of the nighttime and half of the data overall had to be sinus rhythm. Tapes from 152 patients were not analyzed for heart period variability for the reasons listed in Table I.

Frequency domain analysis of normal RR intervals:

After the second stage of editing and review of the results by a cardiologist, the heart period power spectrum

was computed over a 24-hour interval using a method first described by Albrecht and Cohen¹⁰ and adapted by Rottman et al.¹¹ First, a regularly spaced time series was derived from the RR intervals by sampling the irregularly spaced series defined by the succession of normal RR intervals in each 24-hour recording. For each time series 2¹⁸ points were sampled at equal intervals; for a recording exactly 24 hours long, the sampling interval was 329 ms. A "boxcar" low-pass filter with a window twice the sampling interval was then applied. Gaps in the time series resulting from noise or ectopic beats were filled in with linear splines. A fast Fourier transform was computed and the resulting power spectrum was corrected for the attenuating effects of both the filter and the sampling. For a 24-hour recording, the effective frequency range for this method is from 1.157×10^{-5} to 0.800 Hz (periods of seconds to hours). Five frequency domain measures of heart period variability were computed by integrating over their frequency intervals (defined in Table II). In addition, we calculated the ratio of low- to high-frequency power, a measure that has been used as an indicator of sympathovagal balance.³ High values for the ratio indicate predominance of sympathetic nervous activity.

Time domain measures of heart period variability:

From the time series of normal RR intervals, the 6 time domain measures defined in Table II were calculated.

Statistical methods: The frequency distribution of each variable was plotted and assessed for skewness us-

TABLE II Definitions for Time and Frequency Domain Measures of Heart Period Variability

Variable	Domain	Units	Definition
Night-day difference	Time	ms	Difference between the average of all the normal RR intervals at night (24:00 to 05:00) and the average of all the normal RR intervals during the day (07:30 to 21:30)
SDNN	Time	ms	Standard deviation of all normal RR intervals in the entire 24-hour ECG recording
SDANN index	Time	ms	Standard deviation of the average normal RR intervals for all 5-minute segments of a 24-hour ECG recording (each average is weighted by the fraction of the 5 minutes that has normal RR intervals)
SDNN index	Time	ms	Mean of the standard deviations of all normal RR intervals for all 5-minute segments of a 24-hour ECG recording
r-MSSD	Time	ms	Root-mean-square successive difference (the square root of the mean of the squared differences between adjacent normal RR intervals over the entire 24-hour ECG recording)
pNN50	Time	percent	Percentage of differences between adjacent normal RR intervals that are > 50 ms computed over the entire 24-hour ECG recording
Total power	Frequency	ms ²	The energy in the heart period power spectrum up to 0.40 Hz
Ultra low frequency power	Frequency	ms ²	The energy in the heart period power spectrum up to 0.0033 Hz
Very low frequency power	Frequency	ms ²	The energy in the heart period power spectrum between 0.0033 and 0.04 Hz
Low frequency power	Frequency	ms ²	The energy in the heart period power spectrum between 0.04 and 0.15 Hz
High frequency power	Frequency	ms ²	The energy in the heart period power spectrum between 0.15 and 0.40 Hz
LF/HF ratio	Frequency	none	The ratio of low- to high-frequency power

ECG = electrocardiographic; HF = high frequency; LF = low frequency

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ing the value of the standardized third moment around the mean. If the distribution was markedly skewed, i.e., had a skewness coefficient exceeding 1.00, a logarithmic transformation was applied and the new frequency distribution was plotted and examined again. In all cases, the logarithmic transformation did an excellent job of symmetrizing the skewed distributions (see Figure 1) and the log-transformed data were used for those statistical analyses that require data to have a reasonably normal (Gaussian) distribution. We constructed matrices of Pearson product-moment correlation coefficients to evaluate the associations among the measures of heart period variability or between measures of heart period variability and other important predictors of mortality.

When testing hypotheses about the association between 1 or more risk predictors and death, we used the P2L BMDP computer program¹³ to perform Cox proportional hazards analyses.¹⁴ For ease of communication and for eventual clinical use, we dichotomized the 6 time domain measures of heart period variability when estimating their association with mortality. For each, we determined the dichotomization point that maximized the hazard ratio from a Cox regression model¹⁴ for comparing patients below the cut point (expected to be at high risk) with those at or above it (expected to be at low risk).

To determine whether any of the 6 time domain measures of heart period variability was significantly associated with mortality, and to estimate their relative

strengths of association, we evaluated each measure separately, after dichotomization, in a pair of Cox proportional hazards survival models.¹⁴ First, in a univariate analysis, each measure was analyzed as the sole predictor of mortality. Second, 5 covariates known to predict mortality — age, New York Heart Association functional class, rates in the coronary care unit phase of infarction, left ventricular ejection fraction, and 24-hour average frequency of ventricular arrhythmias — were added to the model to test whether the measure of heart period variability predicted mortality independently of the covariates.

For the Cox analysis that adjusted for other risk predictors, the measures of heart period variability were dichotomized to provide ease of interpretation, but the covariates were coded to provide the best fitting model to predict mortality.^{5,15}

Statistical significance was assessed by referring Z , the estimate of the regression coefficient B divided by its standard error, to the standard normal distribution. The strength of association between a measure of heart period variability and a mortality end point was evaluated using $\exp(B)$, which can be interpreted as a relative risk for the given measure.

Mortality end points: We estimated the association between the 6 time domain measures of heart period variability and 3 mortality end points: death from all causes, cardiac death, and arrhythmic death by the Hinkle-Thaler definition.¹⁶ When mortality of all causes was the end point, patients were included in the analysis

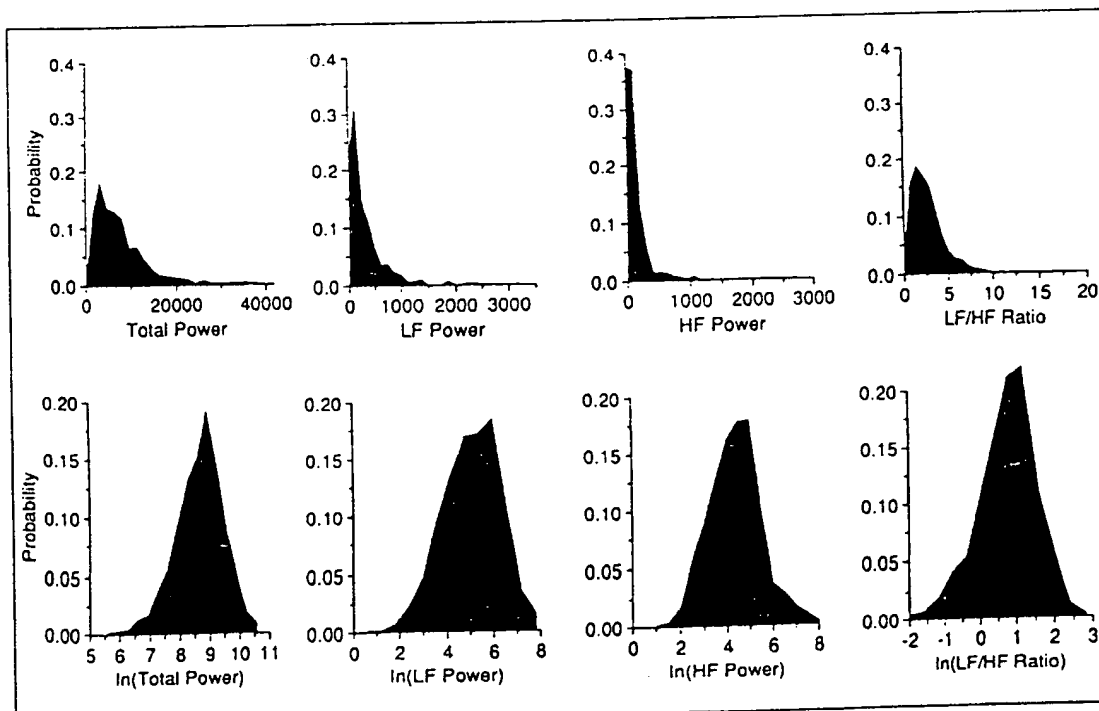


FIGURE 1. The distribution of the components of total power: from left to right, ultra low frequency power (<0.0033 Hz); very low frequency power (0.0033 to 0.04 Hz); low-frequency (LF) power (0.04 to 0.15 Hz); and high-frequency (HF) power (0.15 to 0.40 Hz). top row, frequency distributions with the original units of measurement on the X axis, i.e., ms^2 . The Y axis is the proportion of the 715 patients with the given value on X. Note that the frequency distributions all are skewed to the right. bottom row, frequency distributions of the natural logarithm of the same frequency domain variables. Note that the frequency distributions of the logarithmic transformations have a more Gaussian distribution.

TABLE III Correlations Among Measures of Heart Period Variability (n = 715)

	Night-Day Difference	SDNN	Ln Total Power	Ln ULF Power	SDANN Index	Ln VLF Power	SDNN Index	Ln LF Power	Ln r-MSSD	Ln pNN50	Ln HF Power	Ln LF/HF Power
Night-day difference	1.00											
SDNN	0.71	1.00										
Ln Total power	0.68	0.96	1.00									
Ln ULF power	0.71	0.95	0.99	1.00								
SDANN index	0.75	0.98	0.94	0.96	1.00							
Ln VLF power	0.43	0.78	0.82	0.75	0.68	1.00						
SDNN index	0.44	0.82	0.79	0.71	0.70	0.90	1.00					
Ln LF power	0.42	0.72	0.75	0.67	0.61	0.91	0.89	1.00				
Ln r-MSSD	0.28	0.62	0.58	0.52	0.51	0.60	0.78	0.65	1.00			
Ln pNN50	0.27	0.57	0.56	0.50	0.49	0.59	0.71	0.64	0.93	1.00		
Ln HF power	0.35	0.67	0.66	0.59	0.57	0.70	0.82	0.77	0.92	0.89	1.00	
Ln LF/HF power	0.17	0.20	0.26	0.23	0.17	0.45	0.25	0.49	-0.25	-0.22	-0.18	1.00

Ln = natural logarithm; other abbreviations as in Table II.

as long as they were known to be alive. In analyses of cause-specific mortality, patients who died of other causes were censored at the time they died.

RESULTS

Transformation of heart period variability variables: Figure 1 shows the distributions of the 4 components of total power and illustrates the effect of log transformation in the 715 patients we studied. All of the untransformed frequency domain distributions are positively skewed, as are the distributions for 2 time domain measures, r-MSSD and pNN50 (see explanation in Table II). The distributions of the transformed variables have approximately normal distributions and therefore are suitable for parametric statistical procedures, such as the *t* test, analysis of variance and correlation/regression analyses.

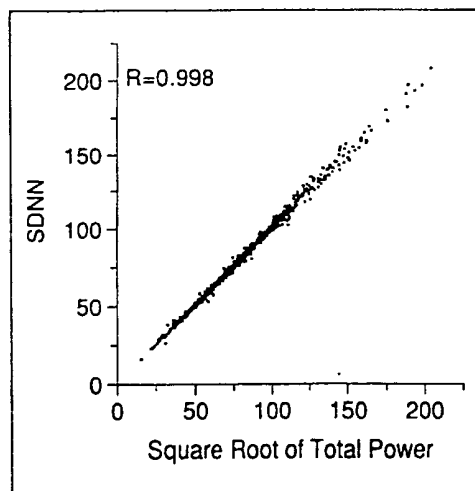


FIGURE 2. The relation between the standard deviation of the normal RR intervals (SDNN) and the square root of total power in the 24-hour heart period power spectrum. The units for both variables are ms. Note that the empirically determined relation is very close to the theoretically expected relation, i.e., intercept of 0 and slope of 1. Also, the correlation coefficient is very close to 1.

Correlations between the measures of heart period variability:

Table III presents correlations between frequency and time domain measures of heart period variability. Power in each band in the frequency domain has a corresponding variable in the time domain that correlates so strongly with it ($r \geq 0.90$) that the 2 variables are essentially equivalent: ultra low frequency power with SDNN and SDANN index, very low frequency power and low-frequency power with SDNN index, and high-frequency power with r-MSSD and pNN50. Correlations this strong between 2 variables suggest that the 2 variables can be used interchangeably when being related to a third variable such as death. As expected from theoretical considerations, SDNN and the square root of total power for a 24-hour interval are almost perfectly correlated (see Figure 2), and the regression line essentially has a slope of 1 and an intercept of 0. This indicates that the manipulation of the data and the calculations involved in the power spectral analysis did not distort the data.

There are 3 natural clusters among 10 of the 12 variables in Table III: (1) SDNN, SDANN index, total power, and ultra low frequency power; (2) very low frequency power, low-frequency power, and SDNN index; and (3) high-frequency power, r-MSSD and pNN50. Interestingly, the ratio of the power in the low-frequency band to the power in the high-frequency band does not correlate strongly with any of the other measures of heart period variability, even those that are used to cal-

TABLE IV Percent of Total Power in the Components of the Heart Period Power Spectrum (n = 715)

Component	Frequency Range (Hz)	Mean \pm SD	Median	Quantile	
				First	Third
ULF power	<0.0033	82 \pm 8	83	77	89
VLF power	0.0033–0.04	12 \pm 6	12	8	16
LF power	0.04–0.15	4 \pm 3	3	2	5
HF power	0.15–0.40	2 \pm 2	1	1	2

Abbreviations as in Table II.

TABLE V Correlation of Measures of Heart Period Variability with Established Postinfarction Risk Predictors and with the Average Normal RR Interval (n = 715)

	Age	NYHA Functional Class	Rales in the CCU	LVEF	Ln (1 + VPC/hour)	Average Normal RR Interval
Night-day difference	-0.22	-0.13	-0.18	0.18	-0.17	0.21
SDNN	-0.22	-0.14	-0.25	0.27	-0.18	0.56
Ln Total power	-0.21	-0.15	-0.27	0.28	-0.20	0.56
Ln ULF power	-0.18	-0.14	-0.25	0.26	-0.19	0.52
SDANN index	-0.28	-0.18	-0.32	0.30	-0.21	0.58
Ln VLF power	-0.18	-0.13	-0.22	0.26	-0.17	0.50
SDNN index	-0.34	-0.18	-0.32	0.31	-0.22	0.48
Ln LF power	-0.31	-0.14	-0.29	0.27	-0.18	0.59
Ln r-MSSD	-0.15	-0.04	-0.17	0.21	-0.12	0.56
Ln pNN50	-0.16	-0.05	-0.17	0.22	-0.13	0.51
Ln HF power	-0.23	-0.08	-0.23	0.25	-0.19	0.57
Ln LF/HF power	-0.20	-0.18	-0.18	0.13	-0.09	-0.04

CCU = coronary care unit; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VPC = ventricular premature complexes; other abbreviations as in Tables II and III.

TABLE VI Cut Points for Time Domain Measures of Heart Period Variability Used for Analysis of Mortality (n = 715)

Variable	Units	Cut Point	Below Cut Point	
			No.	%
Night-day difference in normal RR intervals	ms	40	178	24.9
SDNN	ms	50	103	14.4
SDANN index	ms	40	81	11.3
SDNN index	ms	20	108	15.1
r-MSSD	ms	15	163	22.8
pNN50	%	0.75	130	18.2

Abbreviations as in Table II.

TABLE VII Association of Time Domain Measures of Heart Period Variability with All-Cause, Cardiac and Arrhythmic Mortality

Variable	Mortality					
	All Causes (119 deaths)		Cardiac (88 deaths)		Arrhythmic (68 deaths)	
	Z*	Relative Risk†	Z*	Relative Risk†	Z*	Relative Risk†
Unadjusted for Other Risk Predictors (n = 715)						
Night-day difference	3.41	1.9	2.98	1.9	3.05	2.1
SDNN	5.95	3.3	5.11	3.3	4.57	3.4
SDANN index	6.67	4.0	5.52	3.9	4.68	3.8
SDNN index	5.79	3.2	5.31	3.5	4.43	3.3
r-MSSD	3.08	1.9	3.65	2.3	2.91	2.1
pNN50	3.34	2.0	4.05	2.6	3.28	2.4
Adjusted for Five Other Risk Predictors‡ (n = 673)						
Night-day difference	1.52	1.4	0.79	1.2	1.19	1.4
SDNN	1.99	1.6	1.47	1.5	1.48	1.6
SDANN index	3.23	2.1	2.64	2.0	2.40	2.1
SDNN index	2.19	1.6	1.93	1.7	1.64	1.6
r-MSSD	1.10	1.3	1.59	1.5	1.14	1.4
pNN50	1.48	1.4	2.22	1.7	1.83	1.7

*Z ≥ 1.96, p < 0.05; Z ≥ 2.58, p < 0.01; Z ≥ 3.30, p < 0.001.

†Relative risk = probability of dying if below the cut point/probability of dying if above the cut point.

‡Age, New York Heart Association functional class, rales in the coronary care unit, left ventricular ejection fraction, and frequency of ventricular arrhythmias.

Abbreviations as in Table II.

cause of the small fraction of total power in the low- or high-frequency bands, it is possible to obtain a poor correlation between the power in either of these bands and total power, SDNN, or SDANN.

Correlations between heart period variability and other postinfarction risk predictors: The correlations between time and frequency domain measures of heart period variability and previously identified postinfarction risk predictors are remarkably weak (Table V). No r value even reaches 0.40. This lack of correlation provides ample opportunity for measures of heart period variability to improve the fit of multivariate models for predicting risk of death. The 24-hour average normal RR interval, which is not an important risk predictor, has a modest correlation (r values about 0.50) with all measures of heart period variability except the night-day difference and the ratio of low- to high-frequency power.

Prediction of mortality using time domain variables: Table VI lists the 6 variables we evaluated, their units, their optimal cut points, and the numbers of patients in

the groups categorized as having low values for the variable. Table VII lists, for each measure of heart period variability, the Z scores and relative risks for the association with the 3 mortality end points determined using Cox regression analysis unadjusted for any covariates. All 715 patients were included in this analysis. The measures of heart period variability were dichotomized (Table VI). Each time domain measure of heart period variability had a significant ($p < 0.05$) and most had a strong univariate association (relative risk ≥ 2) with each of the mortality end points. SDANN index, which is strongly associated with ultra low frequency power, had a significant and strong association with all 3 mortality end points. SDNN index, which is strongly associated with very low frequency and low frequency power, also had a significant and strong association with each of the 3 mortality end points. r-MSSD and pNN50, which are strongly associated with high-frequency power, had a significant and moderately strong association with the 3 mortality end points, but the associations were weaker than for the other variables. In a multivariate

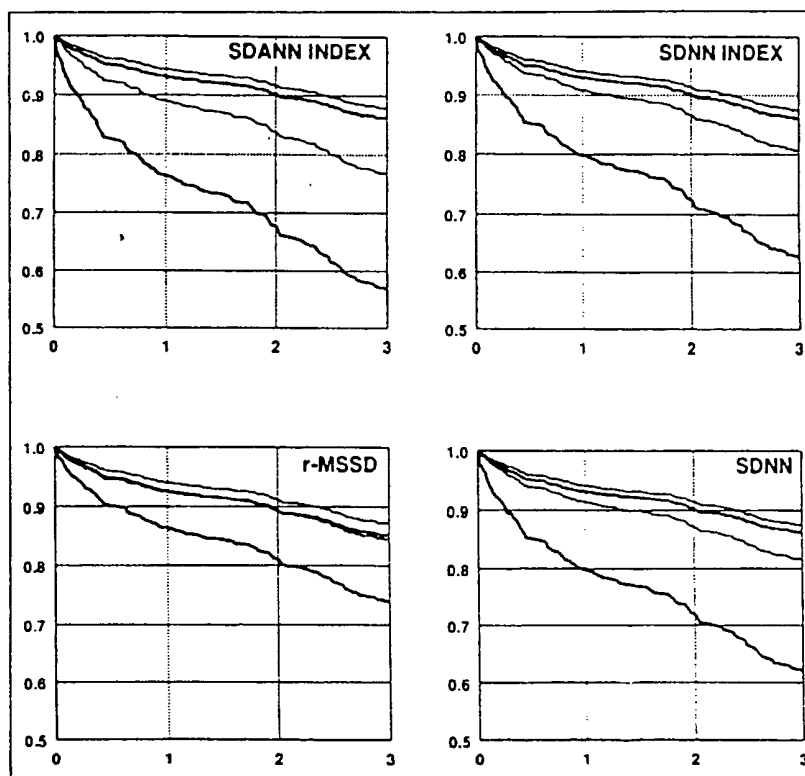


FIGURE 3. Survival curves for patients in the high or low category for 4 time domain measures of heart period variability, SDANN index, SDNN index, and r-MSSD and SDNN, using all-cause mortality as the end point. These curves were fitted by Cox's method for the 673 patients who had adequate Holter data and values for all 5 covariates. Thick lines represent unadjusted heart period variability data, thin lines represent data adjusted for the covariates: age, New York Heart Association functional class, rates in the coronary care unit, radionuclide ejection fraction, and the frequency of ventricular premature complexes. In each panel, the top 2 curves are for patients in the high category and the lower 2 are for patients in the low category. The numbers of patients at the start of follow-up, and the numbers known to be alive and being followed after 1, 2 and 3 years were as follows: high SDANN index (≥ 40 ms) — 596, 546, 506, 228; low SDANN index (< 40 ms) — 77, 60, 49, 21; high SDNN index (≥ 20 ms) — 573, 531, 492, 221; low SDNN index (< 20 ms) — 100, 75, 63, 28; high r-MSSD (≥ 15 ms) — 522, 477, 440, 208; low r-MSSD (< 15 ms) — 151, 129, 115, 41; high SDNN (≥ 50 ms) — 577, 527, 490, 223; low SDNN (< 50 ms) — 96, 78, 65, 26.

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Prediction of mortality using time domain variables adjusting for previously described postinfarction risk predictors: Figure 3 shows survival curves for 4 time domain components of heart period variability calculated using the Cox regression method before and after adjusting for the 5 covariates. Table VII lists, for each measure of heart period variability, the Z scores and relative risks for the 3 mortality end points, determined using Cox regression analysis to adjust for the 5 risk predictor covariates. The 673 patients who had an adequate Holter recording and measurements on all 5 covariates were included in this analysis. Measures of heart period variability were dichotomized (Table VI). After adjustment, some of the variables were no longer significantly associated with mortality. The association between all-cause mortality and SDNN, and SDANN and SDNN indexes remained significant and moderately strong, whereas r-MSSD and pNN50 were only weakly associated with mortality after adjustment.

DISCUSSION

Patterns of correlations among measures of heart period variability: There are strong correlations between frequency and time domain measures of heart period variability. The patterns of correlations are informative. For every band of the 24-hour heart period power spectrum, there is a strong correlation (≥ 0.90) with at least 1 time domain measure of heart period variability, indicating that they may be controlled by similar influences. In the power spectral literature, the physiologic significance of high- and low-frequency power has been delineated. High-frequency power is a pure vagal signal and its frequency is modulated by the frequency of breathing.^{2,3} Low-frequency power is a mixed vagal and sympathetic signal and its amplitude is increased by either increases in vagal tone or increases in sympathetic activity, especially when the autonomic nervous system is participating in arterial baroreflexes.^{2,3} Low- and high-frequency powers have a moderate correlation ($r = 0.77$). In an experiment conducted in normal human subjects, we showed that low- and high-frequency power increase in parallel when vagal tone is increased by atenolol treatment.¹⁷ Also, we showed that low- and high-frequency power decrease in parallel during silent myocardial ischemia in ambulatory patients with known coronary heart disease; this finding was interpreted as withdrawal of vagus nerve activity.¹⁸ These findings suggest that, over a 24-hour period, both low- and high-frequency bands in the heart period power spectrum predominantly reflect parasympathetic

activity. However, short-term measurement (e.g., over 5 minutes) of the heart period power spectrum in conjunction with controlled barostress provides important information about the sympathetic nervous system.^{2,3}

In normal subjects, a change in posture from lying to standing² or head-up tilt from 0° to 90°³ causes a decrease in the high-frequency power and a substantial increase in the ratio of low- to high-frequency power, indicating a decrease in vagal modulation of the RR interval and an increase in sympathetic nervous system activity. This interpretation is strengthened by the response to β -adrenergic blocking drugs which prevent, or markedly attenuate, the increase in the ratio of low- to high-frequency power with postural stress.^{2,3} The findings in this study show that some of the time domain measures of heart period variability also are influenced by autonomic nervous system activity: SDNN index provides similar information to low-frequency power and r-MSSD and pNN50 provide information similar to high-frequency power.

Potential for heart period variability to predict death and its mechanisms after myocardial infarction: Since time domain measures of heart period variability are strongly associated with frequency domain measures (already shown to predict mortality⁵), it is no surprise that time domain measures also predict mortality in the 3 years after myocardial infarction. Which measures of heart period of variability are to be used is largely a matter of objectives and convenience. For risk stratification, ultra low frequency power, very low frequency power, SDNN, SDANN index, and SDNN index provide the best prediction. For mechanistic studies, low-frequency power, SDNN index, high-frequency power, r-MSSD and pNN50 provide insight into the status of the autonomic nervous system.

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